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Novel one-pot synthesis of a library of 2-aryloxy-1,4-naphthoquinone derivatives. Determination of antifungal and antibacterial activity†

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The development of new antibiotics and inexpensive antifungals is an important field of research. Based on the privileged pharmacophore of lawsone, a series of phenolic ether derivatives of 1,4-naphthoquinone were synthesized easily in one step in reasonable yields. All the new compounds were characterized and tested as potential antifungal and antibacterial agents against *Candida albicans*, *Escherichia coli* and *Staphylococcus aureus*. Compound **55** has significant antibacterial action (as good as or better than the controls) against *E. coli* and *S. aureus*. Against *C. albicans*, compounds **38**, **46**, **47** and **60** were the best candidates as antifungals. Using a qualitative structure–activity analysis, a correlation between molar mass and antimicrobial activity was identified, regardless of the substituent group on the phenolic moiety, except for **55** and **63**, where electronic effects seem more important. An *in silico* evaluation of the absorption, distribution, metabolism and excretion (ADME) for **37**, **50**, **55** and **63** was made, indicating that the classic Lipinski's rule of five applies in all cases.

1. Introduction

The treatment of bacterial infections by commercial antibiotics in the past two decades has been threatened by the increasing incidence of multi-drug resistant pathogens. The same can be said of fungal infections by antifungal agents. The misuse and overuse of antibiotics have contributed significantly to this health issue, compromising the public health systems in many countries.[1–3]

Among the most pernicious resistant microbes are *Candida albicans*, *Staphylococcus aureus* and *Escherichia coli*, which are three of the main microorganisms responsible for nosocomial infections by formation of biofilms on medical devices.[4,5] *E. coli* and *S. aureus* are part of the ESKAPE group, an acronym for difficult to treat bacteria that stands for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species.[6–9]

As part of the search for new effective antibiotics and antimicrobials, natural products have played a significant role as structure–activity templates. One family of bioactive natural products, naphthoquinones, are a group of chromatic pigments found inside the vacuoles and as secondary metabolites in some families of plants (Verbenaceae, Bignoniaceae, Lythraceae), bacteria (*Streptomyces*) and fungi (*Fusarium*). These compounds provide protection against microorganisms, acting as pro-oxidants by the production of reactive oxygen species (ROS) through radical chain reactions, and as potential electrophiles when they react with nucleophilic centers in biological molecules to form covalent bonds.[10–12] Examples of common naphthoquinones (Fig. 1) include lapachol **1**, extracted as a yellow solid from the tree bark of the *Tabebuia* species,[13,14] and lawsone **2**, obtained from the leaves of *Lawsonia inermis* (henna) and some trees of the Lythraceae family.[15,16]

Both lapachol and lawsone exhibit antimalarial, anti-cancer, antitrypanosomal, antifungal and antibacterial properties that have been used as natural remedies in indigenous communities,[16,17] and both structures can be modified for the development of new drugs that will potentially present selective and efficient mechanisms against malaria, cancer, bacteria and fungi.[8,18–23]

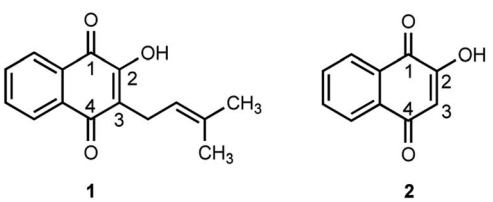

Fig. 1 Lapachol **1** and lawsone **2**, naturally occurring naphthoquinones.

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Fieser and co-workers, in work that extended over a quarter century, determined the physical and chemical properties of lapachol and lawsone and some synthetic derivatives, in order to evaluate their activity against *Plasmodium* species.[24–31] Based on Fieser's seminal work, a series of metal complexes[18,32,33] and C2 and/or C3 naphthoquinone substituted derivatives, such as alkyl,[34,35] nitrogen,[36–43]

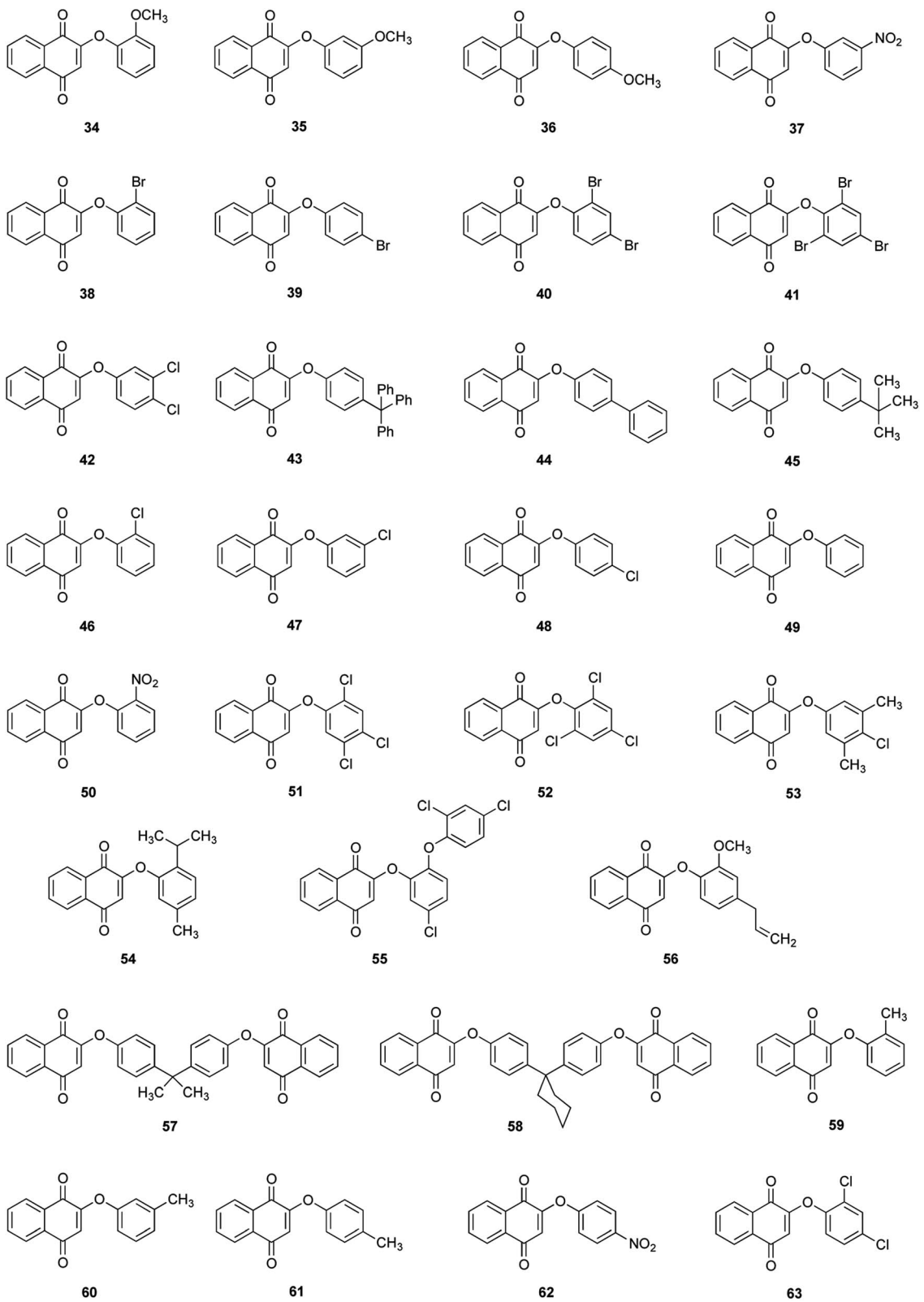


Fig. 2 Synthesized phenolic ether derivatives of 1,4-naphthoquinones.

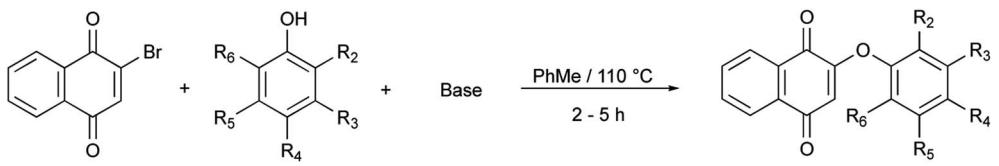
sulfur,[39,41,44–48] and oxygen-containing[21,22,42,49–51] molecules have been proposed as potential antitumoral, antibacterial, antiparasitical, antiviral and antifungal agents.

Among the oxygen-containing compounds are aryloxynaphthoquinones, which include a phenolic or naphtholic moiety. Phenols are important secondary metabolites in plants, because they act as pigments, antioxidants and antimicrobial agents against molds, fungi and bacteria through the modification of the permeability of the cell membrane, modification of the cell wall rigidity or induced changes in intracellular functions.[52–54] Based on the suspected activity of phenolic derivatives, Bolognesi and co-workers have reported the synthesis of a small library of quinone-phenol hybrid compounds, starting with 2-bromo-1,4-naphthoquinone and 2-bromo-1,4-anthraquinone, using dimethylformamide (DMF) as solvent at room temperature and K_2CO_3 as base. The synthesized compounds were tested to determinate their antiparasitic action against *Trypanosoma cruzi*, *T. brucei rhodesiense* and *Leishmania donovani*. Some of these 1,4-naphthoquinone phenolic ethers showed interesting activity.[49] Also, the antitumoral action of these compounds was tested against human dermal fibroblasts, IGROV-1 (ovarian) and HT-29 (colon) adenocarcinoma cells; significant cytotoxic activity was displayed by certain quinone–phenol hybrids. The active compounds had an inhibitory effect on glycolysis and mitochondrial respiration.[22]

Vázquez and co-workers have also synthesized some 2-aryloxynaphthoquinones under basic conditions (K_2CO_3 as base and DMF at room temperature), as well as 7-aryloxyquinolinquinones and 6-aryloxyfuranaphthoquinones, to evaluate their antitrypanosoidal action against the epimastigote form of *T. cruzi*, using nifurtimox as reference compound. Most of the prepared compounds were more active than the reference drug, and those that were more potent, were also more selective in comparison with J-774 cells.[42] In a second study by the same authors, a new set of aryloxyquinones, synthesized under the same reaction conditions, was tested against the epimastigote form of *T. cruzi* in the presence of nifurtimox as reference drug. They discovered that the majority of the synthesized products showed higher potency than the control compound, but only two of them showed high selectivity towards nonneoplastic monkey kidney cells (Vero).[50]

Detailed in this article is our contribution to naphthoquinone research; a library of thirty phenoxy-1,4-naphthoquinone derivatives was prepared *via* a novel one-pot synthesis from 2-bromo-1,4-naphthoquinone (2-BrNQ) combined with the corresponding phenols in the presence of a base (CsOH, Cs_2CO_3 or KF/Al_2O_3) and toluene as solvent, which proceeded through an nucleophilic substitution reaction. The main objective of the study was to evaluate the antimicrobial action of this group of compounds against *C. albicans*, *E. coli* and *S. aureus*, in order to determine a posible correlation between these results and basic structural properties of aryloxy-1,4-naphthoquinones: molar mass and the substitution pattern at the phenolic moiety. Furthermore, an *in silico* evaluation of

Table 1 Reaction conditions, yield, and purity of the synthesized compounds[a]



3 — 1.00 mmol; 4 - 33 — 1.25 mmol; 64 - 66 — 1.5 - 2.0 mmol; 34 - 63 — 1.00 mmol

Compound	Base	Time (h)	Yield (%)	Purity (%)	Compound	Base	Time (h)	Yield (%)	Purity (%)
34	64	2	68	99.9	**49**	64	4	77	98.6
35	64	2	52	95.9	**50**	64	4	30	N.D.
36	64	2	96	99.3	**51**	64	4	26	98.7
37	64	2	58	99.0	**52**	64	4	44	99.3
38	64	2	87	99.7	**53**	64	4	53	98.0
39	64	3	75	99.7	**54**	64	4	58	96.2
40	64	3	62	98.9	**55**	64	4	40	99.1
41	64	3	65	97.3	**56**	64	4	11	97.1
42	64	3	50	98.7	**57**	64	5	56	95.1
43	64	3	82	96.0	**58**	64	5	92	99.1
44	64	3	16	99.4	**59**	65	3	27	96.6
45	64	3	56	98.8	**60**	65	3	69	98.7
46	64	3	58	97.9	**61**	65	3	59	97.9
47	64	3	48	97.9	**62**	66	4	24	97.1
48	64	3	76	99.6	**63**	66	3	56	98.3

[a] N.D. = not determined.

the absorption, distribution, metabolism and excretion (ADME) of the most active compounds was applied, based on the Lipinski's rule of five to establish the druglikeness of the prepared compounds.

2. Results and discussion

2.1 Chemistry

Thirty derivatives of 2-phenoxy-1,4-naphthoquinones (Fig. 2) were synthesized *via* a one-pot nucleophilic substitution reaction between 2-bromo-1,4-naphthoquinone (2-BrNQ) **3** and the corresponding phenolate, which was previously deprotonated by bases such as Cs_2CO_3 **64**, CsOH **65** or KF/Al_2O_3 **66** (Table 1). The synthesis was performed using toluene as solvent, and under a positive nitrogen atmosphere or in the presence of a cellulose thimble with CaH_2 to reduce the incidence of moisture, allowing the reaction to go to completion. In general, the compounds of interest were obtained with low-to-excellent yields (Table 1).

In all cases, a single compound was obtained: the product of the nucleophilic substitution at the *ipso* position, which was confirmed by X-ray crystal diffraction analysis (to be published) and by the presence of a signal around 6.0 ppm (singlet) in the ^{1}H NMR spectrum of the crude reaction mixture, assigned to the hydrogen atom bonded to C3. This regioselectivity is a consequence of the transmission of the electronic effects of the carbonyl groups of the naphthoquinone moiety through the C2–C3 double bond, so that the 2-bromo-1,4-naphthoquinone can be regarded as a vinylogous acyl bromide.[55] The C2 position has a better nucleofuge (–Br), which makes it a more reactive position towards a nucleophilic substitution reaction.

In terms of the kinetic reactivity and the thermodynamic stability of the phenolates, these factors are a result of the nature (electron donating or electron withdrawing) and the location of the substituents in the phenolic moiety.[56,57] The nucleophilicity of the phenols is strongly influenced by their acidity, shape and polarizability, so the reaction conditions were chosen to enhance those properties and to maximize the recuperation of the product from the crude reaction mixture. For instance, the selection of the base depended on the pK_a of the phenols, which is affected by the presence of electron-withdrawing (EW) or electron-donating (ED) groups (either by inductive or mesomeric effects); the former groups provide a more thermodynamically stable and less kinetically reactive phenolate than the latter. In this research, phenols containing one or more strongly electron-withdrawing (–NO_2), weakly electron-withdrawing (–Cl, –Br), weakly electron-donating (alkyl and aromatic groups) and strongly electron-donating (–OCH_3) groups were used, as well as sterically small and bulky substituents, so the resultant interval of reaction yields and reaction times depended on the nucleophilicity of each phenolate.[58,59]

The selection of toluene as the reaction solvent was based on the selective solubility of the aryloxy-1,4-naphthoquinone, 2-BrNQ and the phenol, but not the inorganic salts and the base residue. These solubility differences facilitated the work-up process, in terms of time and steps needed, given that the separation of the compound of interest from the reaction crude only involved a hot filtration step. Initially, aprotic solvents such as DMF and dimethylsulfoxide (DMSO) were considered, as previously reported in the literature,[22,42,49,50] due to the greater solubility of the bases in comparison with non-polar solvents. However, the resulting crude reaction mixtures in DMF consisted of viscous syrups, which were not easy to concentrate or separate by filtration. The isolation of the product from these mixtures involved a series of unit operations (washing, extraction, filtration) that significantly lowered the yield.

The deprotonation of the phenol was the first step of the reaction. To promote this process, the phenol and the appropriate base were stirred under reflux in the reactor and left for 30 min under a dry nitrogen atmosphere or in the presence of a cellulose thimble with CaH_2 (to remove trace water given the high atmospheric humidity levels under which the reactions were performed). As to the selection of the base, in the cases where intermediate or strongly electron-donating groups were present, CsOH or Cs_2CO_3 were chosen as bases. The preference of Cs_2CO_3 over CsOH rests on two criteria: (1) the former's lower hygroscopic character; even a trace of water produced subproducts due to attack on C2 in the naphthoquinone moiety to form lawsone, and (2) because carbonate is a weaker base

Table 2 Antimicrobial activity of the 2-aryloxy-1,4-naphthoquinone derivativs, expressed as minimal inhibitory concentration (μmol L^{-1})

Compound	Molar mass (g mol^{-1})	MIC (μmol L^{-1})		
		S. aureus	*E. coli*	*C. albicans*
34	280.275	3568	892	3568
35	280.275	223	3568	446
36	280.275	1784	3568	3568
37	295.246	21.2	3387	3387
38	329.145	760	3038	190
39	329.145	3038	3038	3038
40	408.041	2450	2450	2450
41	486.937	2054	2054	2054
42	319.139	3133	3133	3133
43	492.563	2030	2030	2030
44	326.345	3064	3064	3064
45	306.355	3264	3264	3264
46	284.694	220	3512	220
47	284.694	878	3512	220
48	284.694	439	3512	439
49	250.249	250	250	4000
50	295.246	13	1693	85
51	353.584	2828	2828	2828
52	353.584	2828	2828	2828
53	312.747	3197	3197	3197
54	306.355	3262	3262	3262
55	445.679	0.34	0.56	2244
56	320.339	1561	3122	3122
57	540.562	925	1850	1850
58	580.626	431	1722	1722
60	264.276	473	3784	237
61	264.276	237	3784	473
62	295.246	212	3387	3387
63	319.139	49	3133	3133
Gentamicin sulphate	1488.8	0.52	0.52	—
Ketoconazole	541.43	—	—	0.56

with negligible nucleophilic character, compared to hydroxide ion.[60–62] On the other hand, Al_2O_3/KF was reserved to the most acidic phenols. Although the pK_a of HF is low ($pK_a = 3.14$), it is suspected that KOH is produced in the early stages of deposition of KF over alumina, hence augmenting the basicity of the resulting material without the concomitant production of free hydroxide ion.[63] K_3PO_4 and K_2CO_3 were also tested as bases, but due to the poor yields obtained and their low solubility in toluene, their use was discarded. In terms of solubility, cesium salts were preferred over other alkaline bases, given that the polarizability of the cesium ion increases their solubility in non-polar solvents.[64]

2.2 Biological activity of the naphthoquinone phenolic ethers

The results of the measured biological activity of the synthesized compounds (in MIC, μmol L^{-1}) are shown in Table 2. From all the synthesized phenolic ethers, the triclosan derivative **55** was the most effective against *S. aureus* and *E. coli* (the MICs were comparable to the control compound, gentamicin sulphate, in a 1.7 and 0.97-fold, respectively), but not for *C. albicans*, so **55** shows significant antibacterial activity, but little antifungal activity against *C. albicans*. These results agree with the known bactericidal action of triclosan, attributed to the inhibition of the enoyl-acyl reductase protein transporting enzyme, which blocks lipid synthesis.[65,66]

In general, except for the triclosan derivative (**55**), the synthesized compounds exhibit a mild-to-low action towards the selected microorganisms, although the antibacterial effect is more significant than the antifungal, given the high MIC values against *C. albicans*. *S. aureus*, a Gram-positive bacteria, proved to be slightly more sensitive to the synthetized compounds than *E. coli* (a Gram-negative bacteria), accordingly to what is reported in the literature for some naphthoquinone derivatives.[41,67] As to the phenolic moiety, the results agree with the reported sensitivity, which is slightly greater towards *S. aureus*. In terms of the reported phenolic antibacterial action, the sensitivity of these microorganisms towards the synthesized compounds agrees with what is reported for some phenols and polyphenols.[52,68–70]

A plot of the MIC *versus* the molar mass of each compound shows an interesting trend, in which the increase of lipophilic

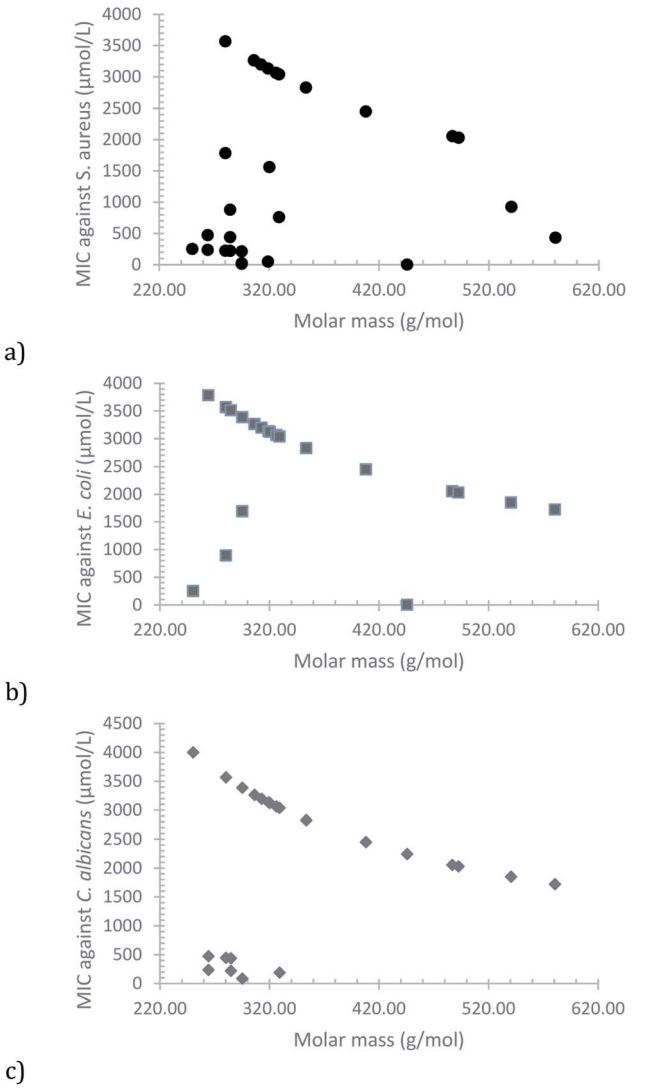


Fig. 3 Observed correlation between MIC and molar mass of the synthesized compounds for (a) *S. aureus*, (b) *E. coli* and (c) *C. albicans*.

Table 3 Assessment of the effect of substituents in the phenolic moiety on the relative antimicrobial action of the synthesized compounds

		$MIC_{49}/MIC_{compound}$		
Compound	Molar mass (g mol^{-1})	*S. aureus*	*E. coli*	*C. albicans*
34	280.275	0.07	0.28	1.12
35	280.275	1.12	0.07	8.97
36	280.275	0.14	0.07	1.12
37	295.246	11.79	0.07	1.18
38	329.145	0.33	0.08	21.05
39	329.145	0.08	0.08	1.32
40	408.041	0.10	0.10	1.63
41	486.937	0.12	0.12	1.95
42	319.139	0.08	0.08	1.28
43	492.563	0.12	0.12	1.97
44	326.345	0.08	0.08	1.31
45	306.355	0.08	0.08	1.23
46	284.694	1.14	0.07	18.18
47	284.694	0.28	0.07	18.18
48	284.694	0.57	0.07	9.11
49	250.249	1.00	1.00	1.00
50	295.246	19.23	0.15	47.06
51	353.584	0.09	0.09	1.41
52	353.584	0.09	0.09	1.41
53	312.747	0.08	0.08	1.25
54	306.355	0.08	0.08	1.23
55	445.679	735.29	446.43	1.78
56	320.339	0.16	0.08	1.28
57	540.562	0.27	0.14	2.16
58	580.626	0.58	0.15	2.32
60	264.276	1.05	0.07	8.46
61	264.276	0.53	0.07	16.88
62	295.246	1.18	0.07	1.18
63	319.139	5.10	0.08	1.28

Table 4 Antimicrobial activity of some monosubstituted 2-aryloxynaphthoquinones at *o*, *m* and *p* positions against *S. aureus*, *E. coli* and *C. albicans*

	MIC (μmol L^{-1})								
	S. aureus			*E. coli*			*C. albicans*		
Substituent group	*o*	*m*	*p*	*o*	*m*	*p*	*o*	*m*	*p*
$-NO_2$	13	21.2	212	1693	3387	3387	85	3387	3387
–Cl	220	878	439	3512	3512	3512	220	220	439
$-OCH_3$	3568	223	1784	892	3568	3568	3568	446	3568

character, due to the greater non-polar section, seems to be the main factor (Fig. 3). Some exceptions are observed (mostly for *S. aureus*), which can be attributed to a greater impact of electronic effects, caused by the position of the substituent in the phenolic moiety and its electron-donor or electron-withdrawing nature.

To assess the effect of the substituent group in the phenolic moiety, in comparison to the unsubstituted compound (**49**), a ratio between the MIC of **49** and the corresponding MIC for each compound, was calculated (Table 3). In general, the presence of substituents seems to affect in a greater extent the action against *C. albicans*, given that all the substituted 2-aryloxynaphthoquinones display a greater MIC ratio, while for *E. coli*, only **55** significantly increases this ratio. For *S. aureus*, electron-withdrawing groups like –Cl and $-NO_2$ demonstrate a greater ratio than electron-donating groups like $-OCH_3$ or $-CH_3$.

In terms of the substituent's position in the phenolic moiety (*o*, *m*, or *p*), the three derivatives of $-NO_2$ (**37**, **50**, **62**), –Cl (**46**, **47**, **48**) and $-OCH_3$ (**34**, **35**, **36**) were considered (Table 4). For *S. aureus*, the presence of substituents in *ortho* and *para* positions exhibits a greater incidence in the activity as the electron-withdrawing effect increases, while for the *meta* position, the presence of weak EW groups like –Cl diminishes the activity, in

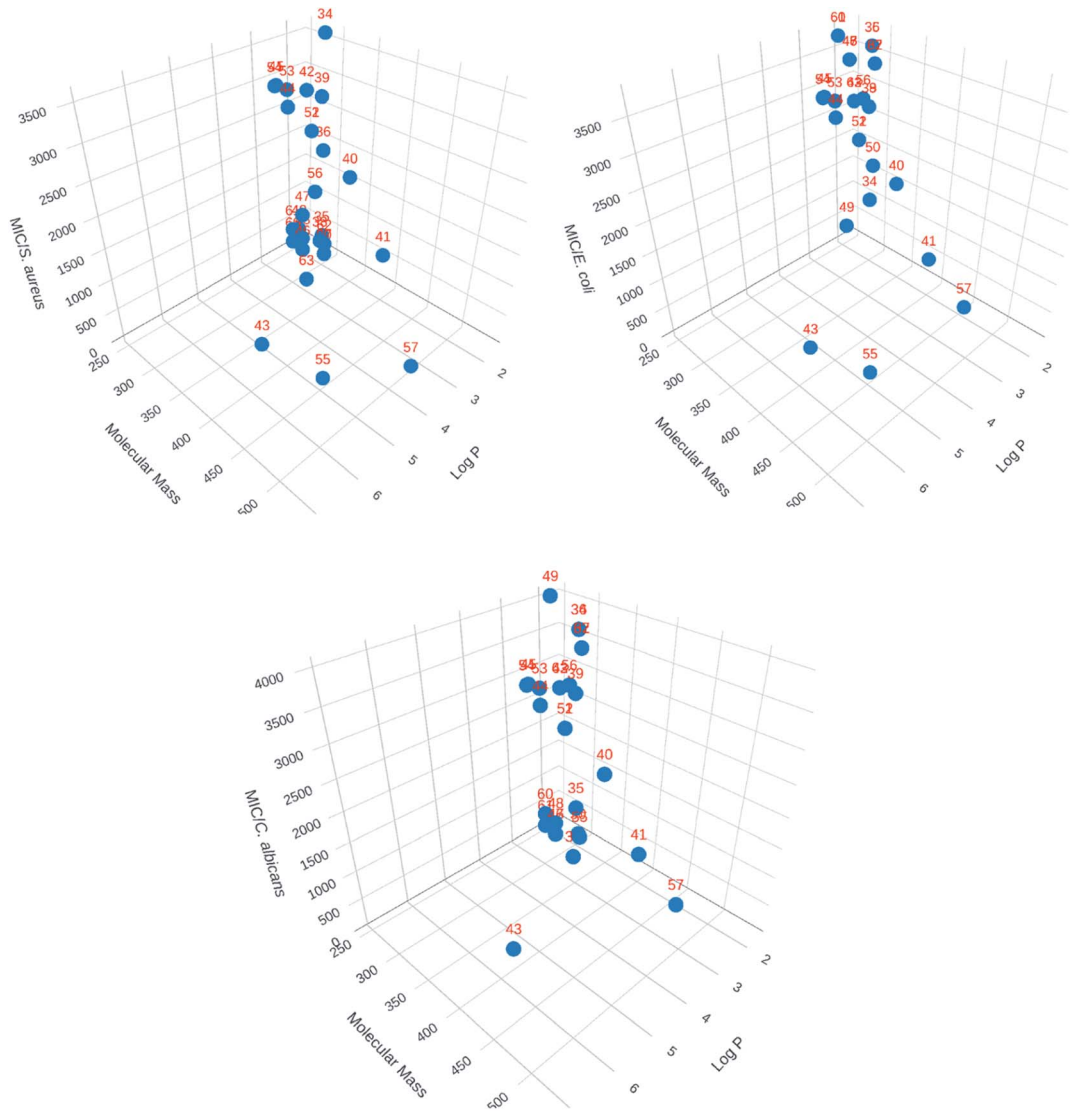


Fig. 4 3D Cartesian correlations for the library of compounds (Plotly Chart Studio online, https://chart-studio.plotly.com/feed/#/).

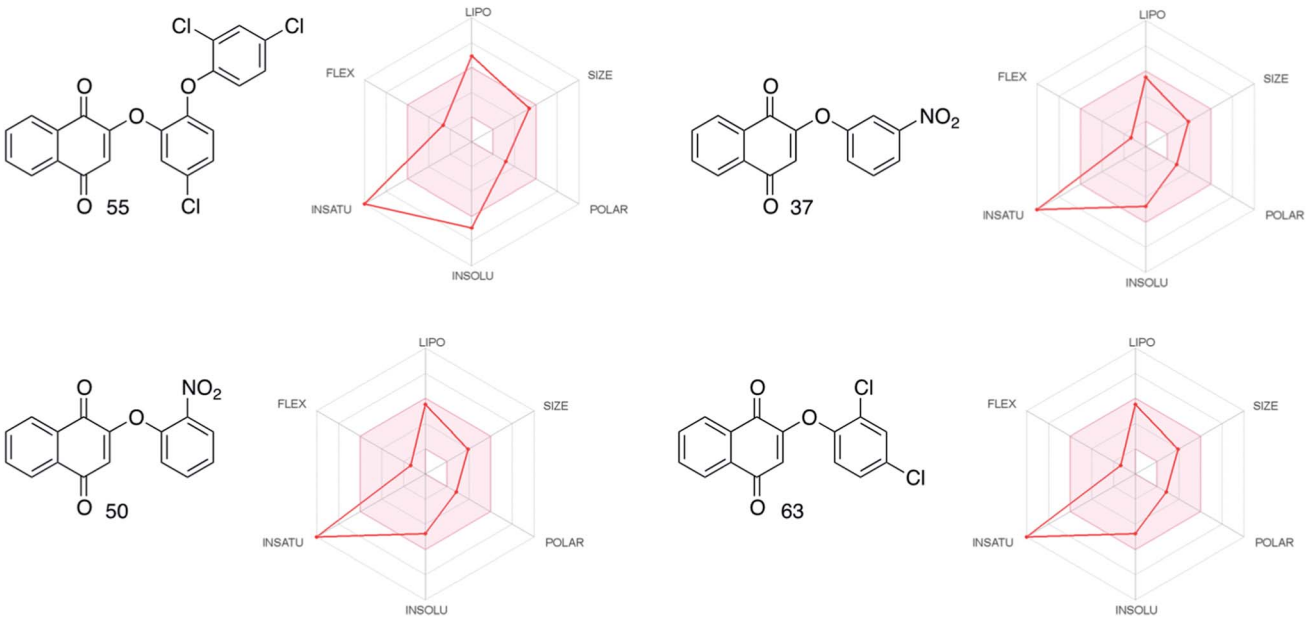


Fig. 5 Radar plots comparison for the most active compounds (SwissADME web tool[71]).

comparison to $-OCH_3$ and $-NO_2$. As to the influence of the *ortho* and *para* positions on the activity, the former shows a greater effect than the latter. It is interesting to point out that the presence of two –Cl groups in *ortho* and *para* positions increases the activity in comparison to the monosubstituted compounds, as **63** is more effective towards *S. aureus* than **46** and **48**.

In the case of *E. coli*, the *meta* and *para* positions do not exert an important effect on the activity regardless of the substituent's nature, while for *ortho*, the presence of an ED group ($-OCH_3$) lowers the MIC, in comparison to a strong EW as $-NO_2$, or a weak EW group as –Cl. As to *C. albicans*, the presence of $-NO_2$ exerts a more significant effect on the activity when it is located at the *ortho* position, while for –Cl, *ortho* and *meta* positions display the same effect, that is slightly greater than the *para* position. In the case of $-OCH_3$, the location at the *meta* position produces an 8-fold increase in the activity when compared to the *ortho* or *para* positions.

3D Cartesian plots were made using Plotly Chart Studio online (**https://chart-studio.plotly.com/feed/#/**) to visualized 3D structural parameters. One of the correlations made is shown in Fig. 4. The value of log *P* were calculated using SwissADME web tool.[71] As seen with the 2D correlations, there is no general tendency that can be drawn besides the fact that compound **55** seems singled out from the rest.

Evaluation *in silico* of the more active compounds (**55**, **37**, **50** and **63**) for their ADME (Absorption, Distribution, Metabolism and Excretion) properties using the SwissADME web tool[71] was performed. The results obtained indicated the drug-likeness of all these phenol ethers, according to the classic Lipinski rule of five. The radar plots (Fig. 5), provided by SwissADME show how the degree of insaturation (INSATU) for a series of aromatic compounds seems to be the most important factor for the drug-likeness of this series (see the ESI† for more details). With further analysis, **55** shows intermediate solubility and lipophilic properties compared to the other three compounds. This behavior may explain the lower drug-likeness of **55** even though it is the most active of the whole group of molecules that have been synthesized.

3. Conclusions

A series of 30 compounds with substituted aryloxy groups connected to the C2 position of 1,4-naphthoquinone were synthesized by an efficient procedure. All the compounds were characterized by spectroscopy and the purity was confirmed by HPLC. The activity of the compounds against selected microorganisms was slight to low, with the exception of the triclosan derivative **55**, which has significant antibacterial action (as good as or better than the controls) against *E. coli* and *S. aureus*. This compound is being further investigated as a potent new antibacterial. In general, for all the compounds, the bactericidal activity is significantly greater against *S. aureus* than against *E. coli*. The fungicidal activity cannot be considered practical, although against *C. albicans*, compounds **38**, **46**, **47** and **60** were the best candidates. We feel that the antibiotic tendencies are worth pursuing with a wider range of compounds whereas the antifungal results show that this pharmacophore is not a viable target against fungi.

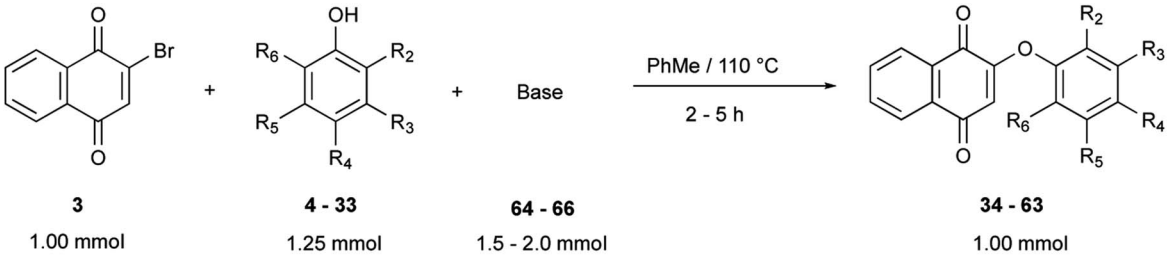
In terms of quantitative structure–activity relationships (QSAR), there is no clear relationship between the activity and the structure of the compound in our library. We showed a general correlation between the activity and molar mass, which seems independent of type of substituent, but further QSAR need to be analyzed to clarify the correlation tendencies. It is interesting that moving away from 'flatland' and using more three-dimensional structures seems to benefit the activity; we are actively pursuing this lead.

The calculated ADME tendencies were ambiguous. Future research will take only the best candidates and run mouse and/or human liver microsomal preparations to determine experimental results. An expanded library of these bioactive compounds will be tested also against other biological strains or pathological microorganisms in the future, including an investigation of the mode of action of these types of compounds.

4. Experimental

4.1 Chemistry

All reagents (except eugenol, bisphenol A and bisphenol Z) were purchased from commercial suppliers [(Sigma-Aldrich-Merck)] and used without further purifications. A Radleys® tube carrousel reaction station (Radleys, UK), was used for the synthesis of the phenolic ethers. Thin-layer chromatography (TLC) was performed using silica gel Kieselgel 60 F_{254} (Merck, Darmstadt, Germany) precoated on aluminum sheets, with fluorescent indicator. Visualization of TLC plates was carried out by means of UV light or I_2 staining. NMR spectra were recorded on a Bruker Ascend spectrometer (^{1}H NMR at 600 MHz, ^{13}C NMR at 150 MHz) at 25 °C, using tetramethylsilane as internal standard for ^{1}H NMR spectra and $CDCl_3$ as solvent for ^{1}H NMR (7.26 ppm) and ^{13}C NMR (77.2 ppm). All chemical shifts were reported in ppm, and the coupling constants (*J*), in Hz. IR spectra were recorded on a PerkinElmer 1000 FT and Varian 640-IR, on KBr pellets and Nujol® mulls. High resolution mass spectrometry spectra were measured on a quadrupole accelerated time-of-flight mass spectrometer (Synapt Acquity UPLC/TOF-MS, Waters). A PerkinElmer Series 200 liquid chromatographer with an UV/Vis detector was used, with a reverse phase C_{18} Discovery® (Supelco Analytical) chromatography column, dimensions of 25 cm × 4.6 mm and a particle size of 5 μm. The solvents employed (MeCN and MeOH) for the determination of the compounds' purity were HPLC grade (LiChrosolv, Merck). The melting point was determined using a Fisher-Johns melting point apparatus. Bisphenol A and bisphenol Z were synthesized according to the procedure described by Rahimi and Farhangzadeh (2001),[72] and their characterization by ^{1}H and ^{13}C NMR agreed with the reported spectroscopic data. For the synthesis of **56**, the corresponding mass of whole cloves



3 1.00 mmol | **4 - 33** 1.25 mmol | **64 - 66** 1.5 - 2.0 mmol | **34 - 63** 1.00 mmol

4: $R_3 = R_4 = R_5 = R_6 = H$, $R_2 = OCH_3$
5: $R_2 = R_4 = R_5 = R_6 = H$, $R_3 = OCH_3$
6: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = OCH_3$
7: $R_2 = R_4 = R_5 = R_6 = H$, $R_3 = NO_2$
8: $R_3 = R_4 = R_5 = R_6 = H$, $R_2 = Br$
9: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = Br$
10: $R_3 = R_5 = R_6 = H$, $R_2 = R_4 = Br$
11: $R_3 = R_5 = H$, $R_2 = R_4 = R_6 = Br$
12: $R_2 = R_5 = R_6 = H$, $R_3 = R_4 = Cl$
13: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = C(Ph)_3$
14: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = Ph$
15: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = C(CH_3)_3$
16: $R_3 = R_4 = R_5 = R_6 = H$, $R_2 = Cl$
17: $R_2 = R_4 = R_5 = R_6 = H$, $R_3 = Cl$
18: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = Cl$
19: R = H
20: $R_3 = R_4 = R_5 = R_6 = H$, $R_2 = NO_2$
21: $R_3 = R_6 = H$, $R_2 = R_4 = R_5 = Cl$
22: $R_3 = R_5 = H$, $R_2 = R_4 = R_6 = Cl$
23: $R_2 = R_6 = H$, $R_3 = R_5 = CH_3$, $R_4 = Cl$
24: $R_3 = R_4 = R_6 = H$, $R_2 = CH(CH_3)_2$, $R_5 = CH_3$
25: $R_3 = R_4 = R_6 = H$, $R_2 = OC_6H_3Cl_2$, $R_5 = CH_3$
26: $R_3 = R_5 = R_6 = H$, $R_2 = OCH_3$, $R_4 = CH_2CHCH_2$
27: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = C(CH_3)_2C_6H_4OC_{10}H_5O_2$
28: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = C_6H_{10}(C_6H_4)OC_{10}H_5O_2$
29: $R_3 = R_4 = R_5 = R_6 = H$, $R_2 = CH_3$
30: $R_2 = R_4 = R_5 = R_6 = H$, $R_3 = CH_3$
31: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = CH_3$
32: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = NO_2$
33: $R_3 = R_5 = R_6 = H$, $R_2 = R_4 = Cl$

64: Cs_2CO_3
65: CsOH
66: KF/Al_2O_3

34: $R_3 = R_4 = R_5 = R_6 = H$, $R_2 = OCH_3$
35: $R_2 = R_4 = R_5 = R_6 = H$, $R_3 = OCH_3$
36: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = OCH_3$
37: $R_2 = R_4 = R_5 = R_6 = H$, $R_3 = NO_2$
38: $R_3 = R_4 = R_5 = R_6 = H$, $R_2 = Br$
39: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = Br$
40: $R_3 = R_5 = R_6 = H$, $R_2 = R_4 = Br$
41: $R_3 = R_5 = H$, $R_2 = R_4 = R_6 = Br$
42: $R_2 = R_5 = R_6 = H$, $R_3 = R_4 = Cl$
43: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = C(Ph)_3$
44: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = Ph$
45: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = C(CH_3)_3$
46: $R_3 = R_4 = R_5 = R_6 = H$, $R_2 = Cl$
47: $R_2 = R_4 = R_5 = R_6 = H$, $R_3 = Cl$
48: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = Cl$
49: R = H
50: $R_3 = R_4 = R_5 = R_6 = H$, $R_2 = NO_2$
51: $R_3 = R_6 = H$, $R_2 = R_4 = R_5 = Cl$
52: $R_3 = R_5 = H$, $R_2 = R_4 = R_6 = Cl$
53: $R_2 = R_6 = H$, $R_3 = R_5 = CH_3$, $R_4 = Cl$
54: $R_3 = R_4 = R_6 = H$, $R_2 = CH(CH_3)_2$, $R_5 = CH_3$
55: $R_3 = R_4 = R_6 = H$, $R_2 = OC_6H_3Cl_2$, $R_5 = CH_3$
56: $R_3 = R_5 = R_6 = H$, $R_2 = OCH_3$, $R_4 = CH_2CHCH_2$
57: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = C(CH_3)_2C_6H_4OC_{10}H_5O_2$
58: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = C_6H_{10}(C_6H_4)OC_{10}H_5O_2$
59: $R_3 = R_4 = R_5 = R_6 = H$, $R_2 = CH_3$
60: $R_2 = R_4 = R_5 = R_6 = H$, $R_3 = CH_3$
61: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = CH_3$
62: $R_2 = R_3 = R_5 = R_6 = H$, $R_4 = NO_2$
63: $R_3 = R_5 = R_6 = H$, $R_2 = R_4 = Cl$

Scheme 1 Synthesis of a series of 2-phenoxy-1,4-naphthoquinones (**34–63**).

(*Syzygium aromaticum*) was used to give approximately 1.25 mmol of eugenol, based on the reported average composition of essential oil.

4.1.1 General procedure I (for the preparation of 34–58). (Scheme 1: base = Cs_2CO_3). 2-Bromo-1,4-naphthoquinone **3** (237 mg, 1.00 mmol) was added to a dry Radleys® tube and the solid was then dissolved in toluene (2 mL). A weighed amount of each phenol **4–28** (1.5 mmol) and Cs_2CO_3 (489 mg, 1.5 mmol) were added to a second dry Radleys® tube, and this mixture was dissolved in toluene (3 mL). Both tubes were placed in a Radleys® carrousel, where constant stirring and reflux were maintained for 30 minutes. After this period, the naphthoquinone solution was slowly added with a Pasteur pipette to the phenolate solution, and the stirring and reflux continued for 2 h (**34–38**), 3 h (**39–47**), 4 h (**48–55**) or 5 h (**56**, **57**). The reaction was monitored by thin layer chromatography (TLC), using toluene as the mobile phase and silica gel (Kieselgel F_{254}, Merck) as the stationary phase. When little or no naphthoquinone substrate was observed on the TLC, the purification step (2.1.4) was applied.

4.1.2 General procedure II (for the preparation of 59–61). (Scheme 1: base = CsOH). 2-Bromo-1,4-naphthoquinone **3** (237 mg, 1.00 mmol) was added to a dry Radleys® tube and the solid was then dissolved in toluene (2 mL). Phenol **29–31** (1.5 mmol) and CsOH (195 mg, 1.20 mmol) were added to second dry Radleys® tube and the mixture was dissolved in toluene (3 mL). Both tubes were placed in a Radleys® carrousel, where constant stirring and reflux were maintained for 30 minutes. After this period, the naphthoquinone solution was slowly added with a Pasteur pipette to the phenolate solution, and the stirring and reflux continued for 3 h. The reaction was monitored by thin layer chromatography, using toluene as the mobile phase and silica gel (Kieselgel F_{254}, Merck) as the stationary phase. When little or no naphthoquinone substrate was observed on the TLC, the purification step (2.1.4) was applied.

4.1.3 General procedure III (for the preparation of 62 and 63). (Scheme 1: base = KF/Al_2O_3 40% m/m). 2-Bromo-1,4-naphthoquinone **3** (237 mg, 1.00 mmol) was added to a dry Radleys® tube and the solid was then dissolved in toluene (2 mL). Phenol **32** and **33** (1.5 mmol) and KF/Al_2O_3 40% (291 mg, 2.0 mmol) were added to second dry Radleys® tube and the mixture was dissolved in toluene (3 mL). Both tubes were placed on a Radleys® carrousel, where constant stirring and reflux were maintained for 30 minutes. After this period, the naphthoquinone solution was slowly added with a Pasteur pipette to the phenolate solution, and the stirring and reflux continued for 3 h (**62**) or 4 h (**61**). The reaction was monitored by thin layer chromatography, using toluene as mobile phase and silica gel (Kieselgel F_{254}, Merck) as stationary phase. When little or no naphthoquinone substrate was observed on the TLC, the purification step (2.1.4) was applied.

4.1.4 Purification of the reaction mixtures

4.1.4.1 Hot extraction–filtration. After the reaction was deemed completed, 10 mL of hot methyl *t*-butyl ether (MTBE), isooctane, *n*-heptane, or dichloromethane (depending on the extraction) were added to the Radleys® reaction tube, and the mixture was then heated up to reflux. The hot solution (red to yellow in color) was filtered by gravity (Whatman #42 filter paper) and the filtrate is collected in a round bottom flask (RBF), while the inorganic salts (black to reddish solids) were retained in the tube or the filter paper. The extraction process was repeated until a clear filtrate was obtained (approx. 4 to 6 times). The filtrate was concentrated under vacuum with a rotary evaporator. The obtained solid product (red to yellow solid) was suspended in cold pentane to dissolve impurities of 2-BrNQ **3**, and the suspension was vacuum filtered to obtain dry product.

4.1.4.2 Cold base wash. After the reaction was deemed completed, the crude reaction mixture was dissolved in MTBE or dichloromethane (15 mL) and the mixture was transferred to a Squibb separatory funnel. The solution was washed five times with 10 mL of cold NaOH 0.5 mol L^{-1} or a saturated cold solution of K_2CO_3 to deprotonate the unreacted phenol. Some phenolate solutions were red, blue, or purple. The combined organic phase was washed with three portions of distilled water to remove any excess of the basic solution, and the organic solution was dried over anhydrous sodium sulfate. The solvent was removed under vacuum with a rotary evaporator. The obtained solid product (red to yellow solid) was suspended in cold pentane to dissolve impurities of 2-BrNQ **3**, and the suspension was vacuum filtered to obtain dry product.

4.1.4.3 Column chromatography. After the reaction was deemed completed, the crude reaction mixture was dissolved in dichloromethane and the solution was transferred to a silica gel (Kieselguhr, 230–400 mesh, Merck) chromatography column. The column was eluted with toluene, cyclohexane, MTBE, dichloromethane, or gradients of solvents, depending on the polarity of the compound and the amount of the phenol residue. The fractions were monitored by TLC and those that contained the product were combined and concentrated with a rotary evaporator. The obtained solid product (red to yellow solid) was suspended in cold pentane to dissolve impurities of 2-BrNQ **3**, and the suspension was vacuum filtered to obtain dry product.

4.1.4.4 Recrystallization. The crude reaction mixture or the treated solid was dissolved in an appropriate hot solvent. The mixture was heated to boiling and then let to cool down to room temperature. Later, the mixture was cooled in a freezer at −20 °C and the suspension of crystals was then vacuum filtered. The obtained solid product (red to yellow solid) was suspended in cold pentane to dissolve impurities of 2-BrNQ **3**, and the suspension was vacuum filtered to obtain dry product.

4.1.5 2-(2-Methoxyphenoxy)-1,4-naphthoquinone (34). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE, cold base wash (MTBE as solvent and NaOH 0.5 mol L^{-1} as base) and recrystallized using isooctane. Yield 141 mg (68%), yellow crystals, mp = (151.0–153.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.21 (1H, d, J = 9 Hz, ArH), 8.06 (1H, d, J = 9 Hz, ArH), 7.75 (2H, m, ArH), 7.28 (1H, t, J_{ortho} = 8 Hz, ArH), 7.13 (1H, d, J_{ortho} = 9 Hz, ArH), 7.03 (1H, t, J_{ortho} = 8 Hz, ArH), 7.00 (1H, d, J_{ortho} = 8 Hz, ArH), 5.85 (1H, s, ArH), 3.80 (3H, s, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.2, 179.7, 159.5, 150.7, 140.9, 134.2, 133.4, 132.1, 131.2, 127.7, 126.7, 126.1, 122.4, 121.4, 113.0, 112.7, 55.7. IR (KBr pellet) cm^{-1}: 3068, 2958, 1683, 1652, 1611, 1499, 1261,

1205. UV-Vis (MeOH) nm: 201, 243 (max), 271, 331. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{17}H_{13}O_4$: 281.0814; found: 281.0819. Purity measured by HPLC: 99.9%.

4.1.6 2-(3-Methoxyphenoxy)-1,4-naphthoquinone (35). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE, cold base wash (MTBE as solvent and NaOH 0.5 mol L^{-1} as base) and recrystallized using isooctane. Yield 109 mg (52%), orange crystals, mp = (84.0–87.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.23 (1H, d, J = 7.5 Hz, ArH), 8.09 (1H, d, J = 7.5 Hz, ArH), 7.80 (2H, m, ArH), 7.38 (1H, t, J_{ortho} = 7.5 Hz, ArH), 6.88 (1H, d, J_{ortho} = 9 Hz, ArH), 6.76 (1H, d, J_{ortho} = 8 Hz, ArH), 6.71 (1H, s, ArH), 6.05 (1H, s, ArH), 3.84 (3H, s, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.0, 179.9, 161.2, 160.4, 153.6, 134.4, 133.5, 132.0, 131.1, 130.8, 126.8, 126.2, 113.5, 113.0, 112.3, 55.5. UV-Vis (MeOH) nm: 211, 244 (max), 270, 331. IR (KBr pellet) cm^{-1}: 3053, 2960, 1678, 1653, 1611, 1584, 1264, 1204. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{17}H_{13}O_4$: 281.0814; found: 281.0812. Purity measured by HPLC: 95.9%.

4.1.7 2-(4-Methoxyphenoxy)-1,4-naphthoquinone (36). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE, chromatography column (CH_2Cl_2 as eluent, isocratic flow) and recrystallized using isooctane. Yield 201 mg (96%), yellow crystals, mp = (133.0–134.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.20 (1H, d, J = 8 Hz, ArH), 8.06 (1H, d, J = 8 Hz, ArH), 7.76 (2H, m, ArH), 7.05 (2H, d, J_{ortho} = 8 Hz, ArH), 6.96 (2H, d, J_{ortho} = 8 Hz, ArH), 5.95 (1H, s, ArH), 3.83 (3H, s, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.0, 179.9, 161.2, 160.4, 153.6, 132.0, 131.1, 126.8, 126.2, 121.1, 117.6, 113.0, 55.5. IR (KBr pellet) cm^{-1}: 3073, 2923, 1680, 1650, 1619, 1503, 1259, 1219. UV-Vis (MeOH) nm: 204, 243 (max), 274, 333. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{17}H_{13}O_4$: 281.0814; found: 281.0817. Purity measured by HPLC: 99.3%.

4.1.8 2-(3-Nitrophenoxy)-1,4-naphthoquinone (37). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with 50% *n*-heptane/toluene and recrystallized using *n*-heptane. Yield 173 mg (58%), yellow crystals, mp = (166.0–167.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.21 (2H, d, J = 6 Hz, ArH), 8.10 (1H, dd, J = 1.2 Hz, J = 6.9 Hz, ArH), 8.04 (1H, t, J_{meta} = 1.2 Hz, ArH), 7.80 (2H, m, ArH), 7.68 (1H, t, J_{ortho} = 8.1 Hz, ArH), 7.52 (1H, ddd, J_{meta} = 1.2 Hz, J_{meta} = 2.3 Hz, J_{ortho} = 8.1 Hz, ArH), 6.05 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.4, 179.3, 159.2, 153.5, 149.4, 134.7, 133.9, 131.8, 131.2, 130.9, 127.1, 127.0, 126.4, 121.3, 116.4, 115.0. IR (KBr pellet) cm^{-1}: 3085, 1676, 1654, 1608, 1527, 1353, 1261, 1222. UV-Vis (MeOH) nm: 209 (max), 241, 272, 331. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{16}H_{10}NO_5$: 296.0559; found: 296.0558. Purity measured by HPLC: 99.0%.

4.1.9 2-(2-Bromophenoxy)-1,4-naphthoquinone (38). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE, column chromatography (1% triethylamine/toluene as eluent, isocratically) and recrystallized using isooctane. Yield 287 mg (87%), yellow crystals, mp = (119.0–121.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.23 (1H, d, J = 6.4 Hz, ArH), 8.08 (1H, d, J = 6.4 Hz, ArH), 7.78 (2H, m, ArH), 7.69 (1H, d, J_{ortho} = 8.6 Hz, ArH), 7.42 (1H, t, J_{ortho} = 8.6 Hz, ArH), 7.22 (1H, t, J_{ortho} = 8.6 Hz, ArH), 7.21 (1H, d, J_{ortho} = 6.4 Hz, ArH), 5.83 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.8, 179.3, 158.7, 149.6, 134.4, 134.3, 133.6, 131.9, 131.0, 129.4, 128.1, 126.8, 126.2, 123.0, 115.6, 113.5. IR (KBr pellet) cm^{-1}: 3068, 1684, 1654, 1612, 1595, 1263, 1225, 660. UV-Vis (MeOH) nm: 203, 209 (max), 215, 249, 271, 333. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{16}H_{10}O_3Br$: 328.9813; found: 328.9806. Purity measured by HPLC: 99.7%.

4.1.10 2-(4-Bromophenoxy)-1,4-naphthoquinone (39). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE and recrystallized using isooctane. Yield 246 mg (75%), yellow needles, mp = (134.0–135.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.20 (1H, dd, J = 2 Hz, J = 6 Hz, ArH), 8.07 (1H, dd, J = 6 Hz, ArH), 7.77 (2H, m, ArH), 7.59 (2H, d, J_{ortho} = 8 Hz, ArH), 7.04 (2H, d, J_{ortho} = 8 Hz, ArH), 5.98 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.7, 179.7, 160.0, 151.8, 134.6, 133.7, 133.5, 131.9, 131.0, 126.8, 126.3, 122.9, 119.8, 113.7. IR (KBr pellet) cm^{-1}: 3095, 1684, 1652, 1612, 1479, 1263, 1232, 717. UV-Vis (MeOH) nm: 221, 249 (max), 269, 335. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{16}H_{10}O_3Br$: 328.9813; found: 328.9814. Purity measured by HPLC: 99.7%.

4.1.11 2-(2,4-Dibromophenoxy)-1,4-naphthoquinone (40). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE and recrystallized using isooctane. Yield 251 mg (62%), yellow solid, mp = (133.0–134.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.21 (1H, dd, J_{ortho} = 7.5 Hz, ArH), 8.08 (1H, dd, J_{ortho} = 7.5 Hz, ArH), 7.84 (1H, d, J_{meta} = 1.9 Hz, ArH), 7.78 (2H, m, ArH), 7.54 (1H, dd, J_{meta} = 1.9 Hz, J_{ortho} = 9.4 Hz, ArH), 7.09 (1H, d, J_{orto} = 7.5 Hz, ArH), 5.84 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.5, 179.1, 158.4, 149.0, 136.7, 134.6, 133.7, 132.5, 131.9, 131.0, 126.9, 126.3, 124.1, 120.4, 116.7, 113.8. IR (KBr pellet) cm^{-1}: 3086, 1686, 1652, 1612, 1465, 1260, 1236, 783, 717. UV-Vis (MeOH) nm: 221, 249 (max), 270, 333. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{16}H_9O_3Br_2$: 406.8918; found: 406.8923. Purity measured by HPLC: 98.9%.

4.1.12 2-(2,4,6-Tribromophenoxy)-1,4-naphthoquinone (41). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with CH_2Cl_2, column chromatography (50% toluene/cyclohexane to dissolve the solid and toluene as eluent, isocratic flow) and recrystallized using methanol. Yield 316 mg (65%), yellow solid, mp = (170.0–172.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.23 (1H, m, ArH), 8.09 (1H, m, ArH), 7.79 (2H, m, ArH), 7.36 (2H, s, ArH), 5.82 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.4, 178.5, 156.4, 148.9, 134.6, 134.2, 133.8, 131.9, 131.0, 126.9, 126.4, 117.8, 113.4, 112.7. IR (KBr pellet) cm^{-1}: 3067, 1684, 1654, 1618, 1593, 1237, 1176, 714. UV-Vis (MeCN) nm: 231, 271 (max). TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{16}H_8O_3Br_3$: 484.8024; found: 484.8034. Purity measured by HPLC: 97.3%.

4.1.13 2-(3,4-Dichlorophenoxy)-1,4-naphthoquinone (42). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE and recrystallized using isooctane. Yield 160 mg (50%), yellow needles, mp = (162.0–163.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.19 (1H, m, ArH), 8.08 (1H, m, ArH), 7.78 (2H, m, ArH), 7.54 (1H, d, J_{ortho} = 8 Hz, ArH), 7.29 (1H, d, J_{meta} = 2 Hz, ArH), 7.03 (1H, dd, J_{meta} = 2 Hz,

J_{ortho} = 8 Hz, ArH), 6.03 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.6, 179.4, 159.5, 151.5, 134.6, 134.1, 133.8, 131.8, 131.8, 130.9, 130.7, 126.9, 126.3, 123.2, 120.5, 114.6. IR (KBr pellet) cm^{-1}: 3069, 1683, 1643, 1624, 1595, 1466, 1265, 1216, 986. UV-Vis (MeOH) nm: 207 (max), 241, 276, 331. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{16}H_9O_3Cl_2$: 318.9929; found: 318.9930. Purity measured by HPLC: 98.7%.

4.1.14 2-(4-Tritylphenoxy)-1,4-naphthoquinone (43). Obtained according to general procedure I 2.1.1, but with less than 1 mmol scale (0.40 mmol of 2-bromo-1,4-naphthoquinone, 0.40 mmol of 4-tritylphenol and 0.60 mmol of dried Cs_2CO_3), and purified by hot extraction–filtration with CH_2Cl_2 and column chromatography (1% triethylamine/toluene as eluent, isocratic flow). Yield 163 mg (82%), light yellow solid, mp = (256.0–257.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.20 (1H, dd, J = 2.0 Hz, J = 7.7 Hz, ArH), 8.08 (1H, dd, J = 2.0 Hz, J = 7.7 Hz, ArH), 7.76 (2H, m, ArH), 7.30 (6H, t, ArH), 7.28 (3H, d, ArH), 7.22 (6H, t, ArH), 7.21 (2H, d, ArH), 7.02 (2H, d, J_{ortho} = 8.3 Hz, ArH), 6.07 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.1, 179.9, 160.3, 150.5, 146.3, 145.4, 134.4, 133.5, 133.2, 132.0, 131.1, 131.0, 127.4, 126.8, 126.3, 126.3, 120.0, 113.3, 64.7. IR (KBr pellet) cm^{-1}: 3059, 1681, 1655, 1600, 1496, 1261, 1225. UV-Vis (MeCN) nm: 218 (max), 245, 269, 331. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{35}H_{25}O_3$: 493.1804; found: 493.1801. Purity measured by HPLC: 96.0%.

4.1.15 2-(4-Phenylphenoxy)-1,4-naphthoquinone (44). Obtained according to general procedure I 2.1.1 and purified by column chromatography (toluene as eluent, isocratic flow) and recrystallized using methanol. Yield 53 mg (16%), beige needles, mp = (199.0–200.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.22 (1H, d, J = 8 Hz, ArH), 8.08 (1H, d, J = 8 Hz, ArH), 7.77 (2H, m, ArH), 7.67 (2H, d, J_{ortho} = 8 Hz, ArH), 7.59 (2H, d, J_{ortho} = 8 Hz, ArH), 7.47 (2H, t, J_{ortho} = 8 Hz, ArH), 7.38 (1H, t, J_{ortho} = 8 Hz, ArH), 7.21 (2H, d, J_{ortho} = 8 Hz, ArH), 6.06 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 185.0, 179.9, 160.5, 152.0, 139.9, 134.5, 133.6, 132.0, 131.1, 129.1, 128.9, 127.7, 127.2, 126.8, 126.3, 121.4, 113.5. IR (KBr pellet) cm^{-1}: 3036, 1683, 1651, 1615, 1593, 1263, 1226. UV-Vis (MeOH) nm: 212, 247 (max), 332. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{22}H_{15}O_3$: 327.1021; found: 327.1021. Purity measured by HPLC: 99.4%.

4.1.16 2-(4-*tert*-Butylphenoxy)-1,4-naphthoquinone (45). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE, column chromatography (toluene as eluent, isocratic flow) and recrystallized using isooctane. Yield 171 mg (56%), yellow needles, mp = (151.0–152.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.22 (1H, d, J = 6 Hz, ArH), 8.06 (1H, d, J = 6 Hz, ArH), 7.77 (2H, m, ArH), 7.46 (2H, d, J_{ortho} = 7 Hz, ArH), 7.05 (2H, d, J_{ortho} = 9 Hz, ArH), 5.97 (1H, s, ArH), 1.35 (9H, s, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 185.1, 180.0, 160.8, 150.2, 149.7, 134.4, 133.5, 132.0, 131.1, 127.2, 126.8, 126.2, 120.4, 113.2, 34.6, 31.4. IR (KBr pellet) cm^{-1}: 3061, 2958, 1678, 1657, 1598, 1504, 1262, 1213. UV-Vis (MeCN) nm: 201, 249 (max), 270, 331. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{20}H_{19}O_3$: 307.1334; found: 307.1335. Purity measured by HPLC: 98.8%.

4.1.17 2-(2-Chlorophenoxy)-1,4-naphthoquinone (46). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE, column chromatography (gradient elution starting with 15% MTBE/cyclohexane to 50% MTBE/cyclohexane) and recrystallized using isooctane. Yield 124 mg (58%), yellow solid, mp = (95.0–96.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.22 (1H, d, J = 7 Hz, ArH), 8.07 (1H, d, J = 7 Hz, ArH), 7.77 (2H, m, ArH), 7.52 (1H, dd, J_{meta} = 3 Hz, J_{ortho} = 8 Hz, ArH), 7.37 (1H, td, J_{meta} = 3 Hz, J_{ortho} = 8 Hz, ArH), 7.29 (1H, td, J_{meta} = 3 Hz, J_{ortho} = 8 Hz, ArH), 7.22 (1H, dd, J_{meta} = 3 Hz, J_{ortho} = 8 Hz, ArH), 5.83 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.8, 179.3, 158.8, 148.5, 134.5, 133.7, 132.0, 131.3, 131.1, 128.7, 127.9, 126.9, 126.7, 126.3, 123.1, 113.4. IR (KBr pellet) cm^{-1}: 3068, 1683, 1653, 1611, 1499, 1261, 1205, 976. UV-Vis (MeOH) nm: 203 (max), 243, 270, 332. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{16}H_{10}O_3Cl$: 285.0318; found: 285.0320. Purity measured by HPLC: 97.9%.

4.1.18 2-(3-Chlorophenoxy)-1,4-naphthoquinone (47). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE, column chromatography (gradient elution starting with 10% MTBE/cyclohexane to 20% MTBE/cyclohexane) and recrystallized using isooctane. Yield 103 mg (48%), yellow solid, mp = (103.0–105.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.20 (1H, d, J = 7 Hz, ArH), 8.08 (1H, d, J = 7 Hz, ArH), 7.78 (2H, m, ArH), 7.40 (1H, t, J_{ortho} = 8 Hz, ArH), 7.31 (1H, d, J_{ortho} = 8 Hz, ArH), 7.17 (1H, s, ArH), 7.06 (1H, d, J_{ortho} = 8 Hz, ArH), 6.00 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.8, 179.6, 159.9, 153.3, 135.7, 134.6, 133.7, 131.9, 131.9, 131.0, 127.0, 126.9, 126.3, 121.7, 119.4, 113.9. IR (KBr pellet) cm^{-1}: 3071, 1681, 1651, 1614, 1585, 1262, 1222, 982. UV-Vis (MeOH) nm: 204 (max), 248, 273, 332. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{16}H_{10}O_3Cl$: 285.0318; found: 285.0323. Purity measured by HPLC: 92.3%.

4.1.19 2-(4-Chlorophenoxy)-1,4-naphthoquinone (48). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE, column chromatography (toluene as eluent, isocratic flow) and recrystallized using isooctane. Yield 162 mg (76%), yellow solid, mp = (131.0–133.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.23 (1H, dd, J = 2 Hz, J = 7 Hz, ArH), 8.11 (1H, dd, J = 2 Hz, J = 7 Hz, ArH), 7.81 (2H, m, ArH), 7.47 (2H, d, J_{ortho} = 6 Hz, ArH), 7.12 (2H, d, J_{ortho} = 6 Hz, ArH), 6.00 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.7, 179.7, 160.1, 151.2, 134.6, 133.6, 132.1, 131.9, 131.1, 130.5, 126.8, 126.3, 122.5, 113.6. IR (KBr pellet) cm^{-1}: 3049, 1684, 1654, 1625, 1482, 1238, 981. UV-Vis (MeOH) nm: 204, 221, 243 (max), 271, 330. TOF-MS: *m*/*z* $[M + H]^+$ calc. for $C_{16}H_{10}O_3Cl$: 285.0318; found: 285.0321. Purity measured by HPLC: 99.6%.

4.1.20 2-Phenoxy-1,4-naphthoquinone (49). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE, cold base wash with MTBE as solvent and NaOH 0.5 mol L^{-1} and recrystallized using h isooctane. Yield 144 mg (77%), yellow-orange crystals, mp = (94.0–102.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.20 (1H, dd, J = 3.4 Hz, J = 6.8 Hz, ArH), 8.07 (1H, dd, J = 3.4 Hz, J = 6.8 Hz, ArH), 7.76 (2H, m, ArH), 7.47 (2H, t, ArH), 7.32 (1H, tt, J_{meta} = 1.3 Hz, J_{ortho} = 7.5 Hz, ArH), 7.14 (2H, d, J_{ortho} = 8.8 Hz, ArH), 5.96 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.0, 179.9, 160.5, 152.7, 134.5, 133.5, 132.0, 131.1, 130.4,

126.8, 126.6, 126.2, 121.1, 113.4. IR (KBr pellet) cm^{-1}: 3067, 1684, 1654, 1614, 1586, 1262, 1213. UV-Vis (MeOH) nm: 210, 244 (max), 270, 331. TOF-MS: m/z $[M + H]^+$ calc. for $C_{16}H_{11}O_3$: 251.0708; found: 251.0703. Purity measured by HPLC: 98.6%.

4.1.21 2-(2-Nitrophenoxy)-1,4-naphthoquinone (50). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with 25% *n*-heptane/75% isooctane and recrystallized using isooctane. Yield 89 mg (30%), yellow crystals, mp = (115.0–118.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.22 (1H, m, ArH), 8.18 (1H, dd, J = 2.6 Hz, J = 6.9 Hz, ArH), 8.08 (1H, m, ArH), 7.78 (2H, m, ArH), 7.75 (1H, m, ArH), 7.51 (1H, m, ArH), 7.33 (1H, dd, J_{meta} = 1.4 Hz, J_{ortho} = 8.2 Hz, ArH), 5.95 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.5, 178.8, 159.4, 146.1, 141.6, 135.4, 134.6, 133.8, 131.9, 131.0, 127.4, 127.0, 126.7, 126.4, 124.4, 114.2. IR (KBr pellet) cm^{-1}: 3072, 1677, 1655, 1602, 1529, 1349, 1264, 1231. UV-Vis (MeOH) nm: 204, 218, 252 (max), 273, 334. TOF-MS: m/z $[M + H]^+$ calc. for $C_{16}H_{10}NO_5$: 296.0559; found: 296.0562. Purity not measured by HPLC.

4.1.22 2-(2,4,5-Trichlorophenoxy)-1,4-naphthoquinone (51). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration and recrystallized, both using *n*-heptane. Yield 92 mg (26%), yellow needles, mp = (158.0–159.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.21 (1H, dd, J = 2.5 Hz, J = 7.6 Hz, ArH), 8.09 (1H, dd, J = 2.5 Hz, J = 7.6 Hz, ArH), 7.79 (2H, m, ArH), 7.65 (1H, s, ArH), 7.35 (1H, s, ArH), 5.93 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.4, 178.8, 158.1, 147.5, 134.7, 133.9, 132.4, 132.0, 131.8, 131.5, 131.0, 126.9, 126.4, 125.8, 124.4, 114.1. IR (KBr pellet) cm^{-1}: 3077, 1686, 1655, 1624, 1466, 1264, 1180, 755. UV-Vis (MeOH) nm: 217, 249 (max), 269, 333. TOF-MS: m/z $[M + H]^+$ calc. for $C_{16}H_8O_3Cl_3$: 352.9539; found: 352.9547. Purity measured by HPLC: 98.7%.

4.1.23 2-(2,4,6-Trichlorophenoxy)-1,4-naphthoquinone (52). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with MTBE and recrystallized using isooctane. Yield 155 mg (44%), yellow needles, mp = (163.0–164.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.23 (1H, m, ArH), 8.08 (1H, m, ArH), 7.78 (2H, m, ArH), 7.46 (2H, s, ArH), 5.82 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.4, 178.5, 156.8, 143.9, 134.6, 133.8, 132.9, 131.9, 131.0, 129.4, 129.3, 126.9, 126.4, 113.2. IR (KBr pellet) cm^{-1}: 3070, 1684, 1654, 1618, 1444, 1260, 1243, 972. UV-Vis (MeCN) nm: 246 (max), 270, 335. TOF-MS: m/z $[M + H]^+$ calc. for $C_{16}H_8O_3Cl_3$: 352.9537; found: 352.9539. Purity measured by HPLC: 99.3%.

4.1.24 2-(4-Chloro-3,5-dimethylphenoxy)-1,4-naphthoquinone (53). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with isooctane, cold base wash with NaOH 0.5 mol L^{-1} and CCl_4 as solvent, and recrystallized using isooctane. Yield 164 mg (53%), yellow-orange crystals, mp = (144.0–145.5) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.20 (1H, dd, J_{ortho} = 7.3 Hz, ArH), 8.07 (1H, dd, J_{ortho} = 7.3 Hz, ArH), 7.76 (2H, m, ArH), 6.88 (2H, s, ArH), 5.98 (1H, s, ArH), 2.40 (6H, s, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.0, 179.8, 160.4, 150.3, 138.7, 134.5, 133.6, 132.4, 131.9, 131.1, 126.8, 126.2, 120.7, 113.5, 20.9. IR (KBr pellet) cm^{-1}: 3068, 2953, 2931, 1686, 1648, 1615, 1596, 1259, 1200, 777. UV-Vis (MeOH) nm: 201, 210 (max), 248, 273, 331. TOF-MS: m/z $[M + H]^+$ calc. for $C_{18}H_{14}O_3Cl$: 313.0631; found: 313.0631. Purity measured by HPLC: 98.0%.

4.1.25 2-(2-Isopropyl-5-methylphenoxy)-1,4-naphthoquinone (54). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with isooctane, cold base wash with NaOH 0.5 mol L^{-1} and CCl_4 as solvent, and recrystallized with isooctane. Yield 178 mg (58%), yellow-orange pellets, mp = (97.0–99.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.21 (1H, m, ArH), 8.07 (1H, m, ArH), 7.76 (2H, m, ArH), 7.27 (1H, d, J_{ortho} = 7.4 Hz, ArH), 7.09 (1H, d, J_{ortho} = 8.4 Hz, ArH), 6.81 (1H, d, ArH), 5.93 (1H, s, ArH), 3.00 (1H, m, CH), 2.35 (3H, s, CH_3), 1.20 (6H, d, –CH(CH_3)$_2$). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.1, 179.9, 160.6, 149.6, 137.6, 137.2, 134.4, 133.5, 132.0, 131.2, 127.8, 127.4, 126.0, 126.2, 121.5, 113.0, 26.7, 23.3, 20.8. IR (KBr pellet) cm^{-1}: 3071, 2953, 1685, 1654, 1607, 1577, 1262, 1194. UV-Vis (MeOH) nm: 218, 249 (max), 272, 332. TOF-MS: m/z $[M + H]^+$ calc. for $C_{20}H_{19}O_3$: 307.1334; found: 307.1339. Purity measured by HPLC: 96.2%.

4.1.26 2-(5-Chloro-2-(2,4-dichlorophenoxy)phenoxy)-1,4-naphthoquinone (55). Obtained according to general procedure I 2.1.1 and purified by hot extraction–filtration with CH_2Cl_2, column chromatography (gradient elution from 100% toluene to 15% diethyl ether/toluene) and cold base wash with NaOH 0.5 mol L^{-1} and CH_2Cl_2 as solvent. Yield 178 mg (40%), ochre solid, mp = (116.0–119.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.15 (1H, dd, J = 1.6 Hz, J = 7.1 Hz, ArH), 8.07 (1H, dd, J = 1.6 Hz, J = 7.1 Hz, ArH), 7.76 (2H, ddd, J_{meta} = 1.6 Hz, J_{ortho} = 7.9 Hz, J_{ortho} = 7.9 Hz, ArH), 7.36 (1H, d, J_{meta} = 1.9 Hz, ArH), 7.28 (1H, d, J_{meta} = 1.9 Hz, ArH), 7.22 (1H, dd, J_{meta} = 1.9 Hz, J_{ortho} = 8.4 Hz, ArH), 7.19 (1H, dd, J_{meta} = 1.9 Hz, J_{ortho} = 8.4 Hz, ArH), 6.91 (1H, d, J_{ortho} = 8.4 Hz, ArH), 6.82 (1H, d, J_{ortho} = 8.4 Hz, ArH), 6.07 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.7, 179.0, 158.4, 149.6, 146.4, 142.6, 134.4, 133.6, 131.9, 131.0, 130.6, 130.5, 129.5, 128.4, 127.6, 126.8, 126.6, 126.3, 123.7, 121.4, 119.5, 114.1. IR (KBr pellet) cm^{-1}: 3067, 1684, 1655, 1619, 1595, 1472, 1260, 1218, 980. UV-Vis (MeCN) nm: 271 (max), 335. TOF-MS: m/z $[M + H]^+$ calc. for $C_{22}H_{12}O_4Cl_3$: 444.9801; found: 444.9804. Purity measured by HPLC: 99.1%.

4.1.27 2-(4-Allyl-2-methoxyphenoxy)-1,4-naphthoquinone (56). Obtained according to general procedure I 2.1.1, except that 3.0 g of whole cloves (*Syzygium aromaticum*) were used to give approx. 1.25 mmol of eugenol. The purification included hot extraction–filtration with diethyl ether and recrystallized using isooctane. Yield 35 mg (11%), ochre solid, mp = (75.0–77.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.20 (1H, d, J = 4.8 Hz, ArH), 8.10 (1H, d, J = 4.8 Hz, ArH), 7.80 (2H, m, ArH), 7.04 (1H, d, J_{ortho} = 4.8 Hz, ArH), 6.85 (1H, s, ArH), 6.82 (1H, dd, J_{ortho} = 4.8 Hz, ArH), 5.98 (1H, m, CH), 5.85 (1H, s, ArH), 5.14 (2H, d, J = 5.7 Hz, =CH_2), 3.78 (3H, s, CH_3), 3.41 (2H, d, J = 6.3 Hz, –CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.3, 179.8, 159.8, 150.6, 140.0, 139.3, 136.8, 134.2, 133.4, 132.2, 131.3, 126.7, 126.1, 122.2, 121.3, 116.4, 113.4, 112.8, 55.8, 40.1. IR (KBr pellet) cm^{-1}: 3068, 2938, 1683, 1650, 1617, 1596, 1503, 1262, 1210. UV-Vis (MeOH) nm: 219, 249 (max), 271, 332. TOF-

MS: m/z $[M + H]^+$ calc. for $C_{20}H_{17}O_4$: 321.1127; found: 321.1122. Purity measured by HPLC: 97.1%.

4.1.28 2-(4-[2-(4-Hydroxyphenyl)propan-2-yl]phenoxy)-1,4-naphthoquinone (57). Obtained according to general procedure I 2.1.1, but using 474 mg (2.0 mmol) of 2-bromo-1,4-naphthoquinone, 228 mg (1.0 mmol) of bisphenol A and 975 mg (3.0 mmol) of dried Cs_2CO_3. The product was purified by hot extraction–filtration with MTBE and recrystallized using toluene. Yield 304 mg (56%), yellow-to-orange solid, mp = (199.0–201.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.20 (2H, d, J = 7 Hz, ArH), 8.06 (2H, d, J = 7 Hz, ArH), 7.76 (4H, m, ArH), 7.33 (4H, d, J_{ortho} = 9 Hz, ArH), 7.07 (4H, d, J_{ortho} = 9 Hz, ArH), 6.01 (2H, s, ArH), 1.73 (6H, s, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.1, 179.7, 160.5, 150.6, 148.6, 134.4, 133.5, 131.9, 131.1, 128.7, 126.8, 126.2, 120.7, 113.3, 42.7, 31.0. IR (KBr pellet) cm^{-1}: 3066, 2974, 1684, 1650, 1597, 1498, 1263, 1216. UV-Vis (MeCN) nm: 251 (max), 271, 334. TOF-MS: m/z $[M + H]^+$ calc. for $C_{35}H_{25}O_6$: 541.1651; found: 541.1664. Purity measured by HPLC: 95.1%.

4.1.29 2-(4-[2-(4-Hydroxyphenyl)cyclohexyl]phenoxy)-1,4-naphthoquinone (58). Obtained according to general procedure I 2.1.1, but using 237 mg (1.0 mmol) of 2-bromo-1,4-naphthoquinone, 200 mg (0.75 mmol) of bisphenol Z and 590 mg (1.6 mmol) of dried Cs_2CO_3. The product was purified by hot extraction–filtration with MTBE and recrystallized using toluene. Yield 251 mg (92%), yellow solid, mp = (248.0–250.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.20 (2H, d, J = 7 Hz, ArH), 8.06 (2H, d, J = 7 Hz, ArH), 7.76 (4H, m, ArH), 7.36 (4H, d, J_{ortho} = 6 Hz; ArH), 7.07 (4H, d, J_{ortho} = 8 Hz, ArH), 6.01 (2H, s, ArH), 2.30 (4H, s, –C(C**H$_2$**CH$_2$)$_2$CH$_2$), 1.59 (2H, m, –C(CH$_2$CH$_2$)$_2$C**H$_2$**), 1.56 (4H, m, –C(CH$_2$C**H$_2$**)$_2$CH$_2$). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.1, 179.9, 160.5, 150.4, 146.6, 134.4, 133.5, 132.0, 131.1, 128.3, 126.8, 126.2, 120.8, 113.3, 46.1, 37.5, 26.2, 22.8. IR (KBr pellet) cm^{-1}: 3058, 2931, 1681, 1652, 1597, 1501, 1262, 1225. UV-Vis (MeCN) nm: 270 (max), 330. TOF-MS: m/z $[M + H]^+$ calc. for $C_{38}H_{29}O_6$: 581.1964; found: 581.1965. Purity measured by HPLC: 93.6%.

4.1.30 2-(2-Methylphenoxy)-1,4-naphthoquinone (59). Obtained according to general procedure II 2.1.2 and purified by hot extraction–filtration with MTBE and column chromatography (1% triethylamine/toluene as eluent, isocratic flow). Yield 70 mg (27%), reddish-brown solid, mp = (79.0–83.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.22 (1H, d, J = 6.8 Hz, ArH), 8.07 (1H, d, J = 6.8 Hz, ArH), 7.77 (2H, m, ArH), 7.31 (1H, d, J_{ortho} = 8 Hz, ArH), 7.28 (1H, td, J_{meta} = 2 Hz, J_{ortho} = 8 Hz, ArH), 7.22 (1H, td, J_{meta} = 2 Hz, J_{ortho} = 8 Hz, ArH), 7.05 (1H, d, J_{ortho} = 8 Hz, ArH), 5.83 (1H, s, ArH), 2.21 (3H, s, –CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.0, 179.9, 159.7, 150.8, 134.4, 133.5, 132.0, 131.2, 130.0, 127.9, 126.8, 126.8, 126.2, 121.2, 112.8, 15.8. IR (KBr pellet) cm^{-1}: 3068, 2927, 1685, 1655, 1613, 1595, 1260, 1226. UV-Vis (MeOH) nm: 213, 249 (max), 268, 332. TOF-MS: m/z $[M + H]^+$ calc. for $C_{17}H_{13}O_3$: 265.0865; found: 265.0865. Purity measured by HPLC: 96.6%.

4.1.31 2-(3-Methylphenoxy)-1,4-naphthoquinone (60). Obtained according to general procedure II 2.1.2 and purified by hot extraction–filtration with MTBE and column chromatography (1% triethylamine/toluene as eluent, isocratic flow). Yield 181 mg (69%), yellow solid, mp = (97.0–102.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.21 (1H, dd, J = 2.1 Hz, J = 6.4 Hz, ArH), 8.07 (1H, dd, J = 2.1 Hz, J = 6.4 Hz, ArH), 7.77 (2H, m, ArH), 7.33 (1H, t, J_{ortho} = 6.4 Hz, ArH), 7.12 (1H, d, J_{ortho} = 6.4 Hz, ArH), 6.95 (1H, d, ArH), 6.93 (2H, d, J_{ortho} = 8.6 Hz, ArH), 5.97 (1H, s, ArH), 2.39 (3H, s, –CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.1, 180.0, 160.6, 152.7, 140.8, 134.4, 133.5, 132.0, 131.2, 130.1, 127.4, 126.8, 126.2, 121.6, 118.0, 113.4, 21.3. IR (KBr pellet) cm^{-1}: 3068, 2927, 1685, 1648, 1607, 1594, 1261, 1245. UV-Vis (MeOH) nm: 212, 248 (max), 270, 333. TOF-MS: m/z $[M + H]^+$ calc. for $C_{17}H_{13}O_3$: 265.0865; found: 265.0863. Purity measured by HPLC: 98.7%.

4.1.32 2-(4-Methylphenoxy)-1,4-naphthoquinone (61). Obtained according to general procedure II 2.1.2 and purified by hot extraction–filtration with MTBE and column chromatography (1% triethylamine/toluene as eluent, isocratic flow). Yield 155 mg (59%), yellow solid, mp = (100.0–102.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.20 (1H, d, J = 5 Hz, ArH), 8.06 (1H, d, J = 5 Hz, ArH), 7.76 (2H, m, ArH), 7.25 (2H, d, J_{ortho} = 7.5 Hz, ArH), 7.01 (2H, d, J_{ortho} = 7.5 Hz, ArH), 5.98 (1H, s, ArH), 2.40 (3H, s, –CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 185.4, 180.0, 160.7, 150.4, 136.4, 134.4, 133.5, 132.0, 131.2, 130.8, 126.8, 126.2, 120.8, 113.2, 20.9. IR (KBr pellet) cm^{-1}: 3072, 2922, 2865, 1679, 1651, 1618, 1506, 1261, 1231. UV-Vis (MeOH) nm: 205, 249 (max), 271, 330. TOF-MS: m/z $[M + H]^+$ calc. for $C_{17}H_{13}O_3$: 265.0865; found: 265.0866. Purity measured by HPLC: 97.9%.

4.1.33 2-(4-Nitrophenoxy)-1,4-naphthoquinone (62). Obtained according to general procedure III 2.1.3 and purified by cold base wash (MTBE as solvent and K_2CO_3 sat as base), column chromatography (toluene as eluent, isocratic flow) and recrystallization with isooctane. Yield 71 mg (24%), brown to yellow crystals, mp = (190.0–192.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.36 (2H, d J_{ortho} = 7.5 Hz, ArH), 8.20 (1H, d, J_{8-7} = 7.5 Hz, ArH), 8.11 (1H, d, J_{5-6} = 7.5 Hz, ArH), 7.81 (2H, m, ArH), 7.30 (2H, d, J_{ortho} = 7.5 Hz, ArH), 6.18 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.4, 179.2, 158.6, 158.1, 145.4, 134.8, 133.9, 131.7, 130.9, 126.9, 126.4, 126.2, 121.1, 116.2. IR (KBr pellet) cm^{-1}: 3050, 1686, 1646, 1616, 1587, 1514, 1340, 1229, 886. UV-Vis (MeOH) nm: 203, 250, 269 (max). TOF-MS: m/z $[M + H]^+$ calc. for $C_{16}H_{10}NO_5$: 296.0559; found: 296.0592. Purity measured by HPLC: 97.1%.

4.1.34 2-(2,4-Dichlorophenoxy)-1,4-naphthoquinone (63). Obtained according to general procedure III 2.1.3 and purified by hot extraction–filtration and recrystallization, both with isooctane. Yield 177 mg (56%), yellow needle crystals, mp = (127.0–130.0) °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.21 (1H, dd, J = 2.5 Hz, J = 6.7 Hz, ArH), 8.08 (1H, dd, J = 2.5 Hz, J = 6.7 Hz, ArH), 7.78 (2H, m, ArH), 7.54 (1H, d, J_{meta} = 2.3 Hz, ArH), 7.35 (1H, dd, J_{meta} = 3.0 Hz, J_{ortho} = 8.3 Hz, ArH), 7.16 (1H, d, J_{ortho} = 8.3 Hz, ArH), 5.84 (1H, s, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 184.6, 179.1, 158.5, 147.2, 134.6, 133.7, 132.9, 131.9, 131.1, 131.0, 128.9, 127.6, 126.9, 126.4, 123.9, 113.6. IR (KBr pellet) cm^{-1}: 3094, 1685, 1653, 1613, 1474, 1262, 1242, 982. UV-Vis (MeOH) nm: 219, 249 (max), 268, 333. TOF-MS: m/z $[M + H]^+$ calc. for $C_{16}H_9O_3Cl_2$: 318.9929; found: 318.9928. Purity measured by HPLC: 98.3%.

4.2 Determination of the purity of the synthesized compounds by HPLC

Solutions (500–1000 μmol L^{-1}) of each prepared compound, the corresponding phenol and 2-BrNQ **3** were separately prepared in 10.00 mL volumetric flasks by the direct method, weighting the required mass of compound on the analytical balance to 4 decimals. In some cases, to complete the dissolution of all the solids, the flask with solvent was placed in an ultrasonic bath and sonicated until the solid dissolved completely. The solutions were filtered through a nylon syringe filters 4.6 cm × 0.20 μm (Agilent), and the filtrate was collected in a vial. 10 μL of the solution were injected in the liquid chromatograph. The elution was perform using an isocratic flow of 1 mL min^{-1} and total elution time of 25 minutes. The wavelengths used were 269 nm (**36–45**, **48**, **49**, **52**, **53**, **55–58**, **62**, **63**), 274 nm (**34**, **51**, **60**) and 286 nm (**35**, **46**, **47**, **54**, **59**, **61**). MeCN (100%) was used as eluent at 269 nm and 274 nm, and a mixture of 40% water/methanol at 286 nm. The purity was determined as the percentage ratio of the area of the compound's peak and the total area.

4.3 Antimicrobial assays of the synthesized compounds against *C. albicans*, *E. coli* and *S. aureus via* the diffusion method[73–75]

4.3.1 Biological assay – microorganisms, media and inocula. For the antimicrobial evaluation, strains from the American Type Culture Collection (ATCC), Rockville, MD, USA, were used. Bacteria used were *Escherichia coli* ATCC 11775, *Staphylococcus aureus* ATCC 6538P, and yeast *Candida albicans* ATCC 10231.

The bacteria used were cultivated on Mueller-Hinton agar (MHA – Difco) at 35 °C for 24 h. Cell suspension in saline (0.86%) was adjusted to give a final concentration of 1.5 × 10^8 cell per mL, standardized with 0.5 on the McFarland scale (λ = 530 nm).[76] The fungi were cultivated on Sabouraud dextrose agar (SDA-Difco). The yeast was prepared according to Pfaller *et al.* (1988),[77] adjusting the suspension to give a final concentration of between 1.0 × 10^6 and 5.0 × 10^6 cell per mL, also standardized with 0.5 on the McFarland scale (λ = 530 nm).

4.3.2 MIC determination and experimental conditions. The minimum inhibitory concentration (MIC) was determined for the organisms by the agar dilution method, which was carried out on slants (1 mL). Stock solutions of each compound in dimethylsulfoxide (DMSO) were diluted to give serial two-fold dilutions which were added to each medium (MHA for bacteria and SDA for yeast), resulting in concentrations ranging from 1000 to 1.95 μg mL^{-1}. A volume of 1 μL of inoculum suspension, prepared previously, was inoculated with a sterile loop to each slant, except for the sterile control. The antibacterial and antifungal agents, gentamicin sulfate (Sigma G3632, USA) and ketoconazole (Sigma K1003, USA), respectively, were included in the assay as positive control. The final concentration of DMSO in the assay did not exceed 2%. A drug-free saline solution (0.86%) was used as a blank control. Each assay was repeated three times. The slants were incubated at 35 °C for the bacteria and yeast. MICs were visually recorded at 24 h for bacteria and 48 h for yeast.

Author contributions

The manuscript was written through contributions of all authors.

Declarations of interest

The authors have no competing financial interests to declare.

Conflicts of interest

There are no conflicts to declare.

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